

REMARKS

Preliminary Remarks

Claims 1, 2, 3, 4, and 5 are amended herein. Claims 10-16 are newly added. Support for the amendments and new claims can be found throughout the specification. For example, support within the specification is found at least at pages 4-7. Thus, the amendments do not represent new matter.

A. The Claims Are Supported By An Adequate Written Description

The Examiner rejected claims 1-9 under 35 U.S.C. § 112, first paragraph, for an asserted lack of written descriptive support. In support, the Examiner asserted that the claimed methods encompass administration of an HSV comprising any modification in an inverted repeat region that results in expression of a single $\gamma_{134.5}$ gene. (Office Action at pages 2-3.) The Examiner further states that the claims embrace an "enormous number of different modified HSVs," but the specification describes one particular modification of an HSV inverted repeat region that results in only one $\gamma_{134.5}$ gene remaining intact (Office Action at page 3.) Additionally, the Examiner continues to rely on The Regents of the Univ. of Cal. v. Lilly, 119 F.3d 1559 (Fed. Cir. 1997), and asserts that a representative number of species have not been described, which the Examiner acknowledges to be dependent on recognition, by one of skill, that the inventors were in possession of the "common attributes or features" of the members of the claimed genus. (Office Action at page 4; emphasis in original.) In response, Applicants traverse.

Statutory law requires that the specification shall contain a written description of the invention. 35 U.S.C. § 112, first paragraph. The courts have interpreted that provision as requiring that the description of the invention be sufficient to allow one of skill in the art to recognize that applicants were in possession of the subject matter claimed. Vas-Cath v. Mahurkar, 935 F.2d 1555 (Fed. Cir. 1991); *accord*, M.P.E.P. § 2163 (I). Further, possession is shown by describing the claimed invention with all of its limitations, such as by describing an actual reduction to practice. M.P.E.P. § 2163 (I).

In the "Summary of the Invention," Applicants provide the following description of the claimed subject matter:

The present invention provides methods for treating cancer comprising the steps of administering . . . a modified HSV

genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome. In one embodiment, methods of the invention include use of HSV strains wherein the modification of the inverted repeat region of the genome comprises an alteration of a copy of a γ 134.5 gene that renders that copy of the gene incapable of expressing an active gene product.

Specification at page 4, lines 9-16. Moreover, in the working examples, Applicants describe an actual reduction to practice of the claimed subject matter in the form of a method of administering an HSV having a modification in an inverted repeat region that comprises an alteration of a γ 134.5 gene. That alteration eliminates expression of an active gene product from that copy of the gene. Applicants additionally note that HSV is a virus that has been characterized, including the characterization of the structure of HSV in terms of its complete polynucleotide sequence and the presence of inverted repeats, and the Examiner has not contended to the contrary. Please see U.S. Patent No. 4,859,587 (Appendix A) and Chou et al., J. of Virol., 68(12):8304-8311, 1994 (Appendix B).

In the application as filed, therefore, Applicants expressly described the invention as methods for treating cancer comprising administering an HSV with a modification to an inverted repeat region. Applicants did not describe the invention as a method of administering an HSV comprising a single expressible copy of the γ 134.5 gene; that subject matter was expressly described as an embodiment of the invention. Accordingly, Applicants submit that the Examiner's focus was misplaced in stating that "the specification describes one particular modification of an HSV inverted repeat region that results in only one γ 134.5 gene remaining intact" The application goes beyond the description of that embodiment to provide a written description of the full scope of the invention as defined in the presently pending claims.

Applicants respectfully submit that the Examiner also erred as a matter of law in misplacing reliance on Lilly, 119 F.3d 1559 (Fed. Cir. 1997). The Lilly Court held that a description of the polynucleotide sequence of a rat cDNA did not provide a written description of either all mammalian cDNAs encoding insulin or of human cDNAs encoding insulin. Lilly reasoned that possession of the rat cDNA did not give the applicant possession of all mammalian cDNAs or of human cDNAs encoding insulin. In contrast, the present claims are drawn to methods of administering a known HSV having a modified inverted

repeat, such as a modification resulting in a single expressible $\gamma_134.5$ gene. Applicants exemplified the claimed invention by describing methods of administering the modified HSV having a single expressible $\gamma_134.5$ gene, but this description is not analogous to the disclosure of the rat cDNA encoding insulin in Lilly. First, the instant applicants expressly defined the invention as methods involving an HSV modified in an inverted repeat region, not just in a region resulting in loss of expression from one $\gamma_134.5$ gene. Second, and perhaps more importantly, the structures of the modified HSVs used in the presently claimed methods were described, unlike the failure to describe all mammalian, or even human, cDNAs encoding insulin at issue in Lilly. The complete structure of unmodified HSV was well known in the art, and the Examiner has not disputed that fact. The inverted repeat regions to be modified were also known in the art. Further, modifications to these regions, such as deletions, insertions, or substitutions of nucleotides, were conveyed to one of ordinary skill by the instant specification coupled with the knowledge in the art. Given the significance of these factual distinctions, Lilly is not probative on the issue of written descriptive support in the present case and the Examiner's continued reliance thereon is misplaced. Moreover, one of ordinary skill in the art would recognize that applicants had possession of the full scope of the claimed methods, and not simply one embodiment thereof.

For all of the foregoing reasons, Applicants submit that the Examiner has erred both factually and legally in maintaining a rejection of the pending claims under 35 U.S.C. § 112, first paragraph, for lack of written description. The claimed subject matter is supported by an express description of the full scope of the invention and one of skill in the art would recognize that Applicants possessed that subject matter at the time of filing. Accordingly, the rejection of claims 1-9 has been overcome and should be withdrawn. Moreover, an analogous rejection of any of new claims 10-16 under § 112, first paragraph, for lack of written description, would be improper for the reasons provided above.

B. The Claims Are Enabled Throughout Their Full Scope

The Examiner rejected claims 1-9 under 35 U.S.C. § 112, first paragraph, for asserted lack of enablement, stating that the specification does not reasonably provide

enabling support for administering the therapeutic HSVs via any route of administration and does not reasonably enable methods of treating by administering an HSV comprising any modification in an inverted repeat region. In response, Applicants traverse.

Applicants respectfully submit that the Examiner has misperceived the significance of the Kooby and Walker references, cited by Applicants in their prior response to address the Examiner's assertion that Example 2 of the specification only enabled direct administration of the modified HSV. (See Office Action mailed October 11, 2002, at pages 10-11.) Based in part on that misperception of Kooby and Walker, a *prima facie* case of non-enablement has not been established for any of the rejected claims. In addressing Applicants' citations to Kooby and Walker, the Examiner noted that these references disclosed administrations of HSVs modified such that there was no expressible $\gamma_{134.5}$ gene, rather than an elimination of the expression of one $\gamma_{134.5}$ gene. The Examiner concluded that Kooby and Walker disclosed methods that differed from the claimed methods and that the Kooby and Walker methods didn't share the deleterious potential effect on non-cancerous cells expected of the claimed methods. Applicants emphasize that Kooby and Walker were not cited as disclosing the claimed method. Rather, these references confirm the assertion that HSV, including modified HSV, may be effectively administered by any number of routes. Thus, one of skill in the art would reasonably expect the modified HSVs recited in the pending claims to be deliverable by any known route, and the Examiner has not provided evidence inconsistent with that position. Rather, the Examiner has focused on the potential effects of such modified HSVs on non-cancerous cells and asserted that such effects would not be shared by the modified HSVs of Kooby or Walker. That assertion is not relevant to the question of enablement, however. The effect of a modified HSV on a non-cancerous cell is not relevant to whether the specification provides enabling support for methods of treating cancer cells by administering the claim-recited HSVs by any known administration route. In view of the disclosures in the specification, the confirming disclosures of Kooby and Walker relating to the administration routes suitable for delivery of modified HSVs, and the lack of relevance of HSV effects on non-cancerous cells in determining administration routes for treating cancer cells, Applicants submit that the claimed subject matter is supported by an enabling disclosure commensurate in scope to the pending claims, and the Examiner's observations do not challenge that position.

The Examiner also asserts that the full scope of the claims is not enabled in terms of the various modified HSVs that may be used in the claimed methods. In the Office Action, the Examiner's supporting remarks are limited to the following assertion: "However, the Applicants arguments with respect to the routes of administration and to the administration of any modified HSV encompassed by the claims (other than the one specifically described) are not persuasive." (Office Action at page 6.) The Examiner also relied on reasons of record. In response, Applicants disagree with the Examiner and assert that each of the modified HSVs recited in the pending claims was specifically described in the application as filed, not just the specific embodiment exemplified in the working examples. As noted above, the HSV structure was known in terms of its complete polynucleotide sequence and the inverted repeat regions. Methods for modifying inverted repeat regions of those polynucleotides such that only one gene (e.g., $\gamma_{134.5}$ gene) remained intact or expressible, were known in the art. Thus, one of ordinary skill in the art could have made or used the claimed methods throughout their full scope. To maintain otherwise would be to argue, for example, that in the chemical arts, one has not enabled a useful polymer such as nylon or polyethylene if one has not provided the complete structure of each molecule, such as by failing to indicate the exact length of each polymeric molecule.

Beyond the preceding remarks, Applicants note that an enablement inquiry is guided by a consideration of a number of relevant factors identified in the law. The Applicants submit that a consideration of these factors leads to the conclusion that they have satisfied the enablement requirement by providing sufficient disclosure to teach one of skill in the art how to make and use the claimed invention without requiring undue experimentation. The statute does not require "a specific example of everything within the scope of a broad claim." *In re Anderson*, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973). What constitutes undue experimentation depends upon a number of factors, which include the quantity of experimentation necessary, the nature of the invention, the amount of direction or guidance presented, the presence of working examples, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 U.S.P.Q. 546 (Bd. Pat. App. and Int'f (1986); *see also In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. (1988)).

In the instant case, the quantity of required experimentation is insignificant because the reference polynucleotide sequence of HSV was known and the Applicants taught that the region to be modified was the inverted repeat region and taught that the result of the modification would be to leave one gene ($\gamma_134.5$) intact. Moreover, modifications in the form of substitutions, deletions and insertions are amenable to any of a wide number of well-known molecular techniques and the Applicants have taught the result (one intact gene).

The preceding remarks also establish that Applicants have provided considerable guidance in identifying modified HSVs suitable for use in the claimed methods. This guidance, coupled with the knowledge in the art, provides sufficient direction to allow one of skill to construct, test and identify (i.e., make), as well as use, the claimed methods comprising the modified HSVs recited in those claims. Another factor weighing in favor of concluding that the claims are enabled is the relatively high level of skill of those in the art, and the Examiner has not taken a contrary position with respect to this factor. Finally, the Applicants submit that the breadth of the claims also favors a determination that the claims are enabled because the claims are tailored to the inventive subject matter disclosed in the application, i.e., particular methods of treating particular diseases by reducing tumor masses using particular HSVs modified in an inverted repeat region such that one copy of an identified gene expresses an active gene product.

For the foregoing reasons, the Applicants submit that the rejection of claims 1-9 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been overcome and should be withdrawn. For analogous reasons, a rejection of any of new claims 10-16 under § 112, first paragraph, for lack of enablement would be improper.

C. The Claims Use Definite Language

The Examiner rejected claims 1-9 under 35 U.S.C. § 112, second paragraph, as indefinite in reciting that "only one $\gamma_134.5$ gene remains intact." (Office Action at page 8; emphasis in original.) The Examiner further asserted that the term "intact" was indefinite in that it is unclear if a modification consisting of a conservative substitution would result in an "intact" $\gamma_134.5$ gene. In response, although Applicants submit that the term "intact," when construed in view of the specification as a whole, is not indefinite, the claims have been

effectively amended to clarify the claimed subject matter without altering the scope of any claim.

In support of the position that "intact" is not indefinite, Applicants cite to the first paragraph of the "Summary of the Invention" section of the application, quoted at greater length above, which recites that "[t]he present invention provides methods for treating cancer comprising the steps of administering . . . a Herpes simplex virus (HSV) comprising a modified HSV genome wherein . . . the modification of the inverted repeat region of the genome comprises an alteration of a copy of a γ 134.5 gene that renders that copy of the gene incapable of expressing an active gene product." (Specification, page 4, lines 9-16.) Thus, the HSV modifications that eliminate the intact character of one γ 134.5 gene are modifications that render the gene incapable of expression. Given this meaning, a conservative substitution that did not render one copy of a gene incapable of expression would not be a modification in accordance with the present invention.

To advance the prosecution of this application, however, Applicants have effectively amended the claims, as noted above. Amended claim 1 recites that "only one γ 134.5 gene expresses an active gene product." This amendment clarifies the claim language and is in complete agreement with Applicants' explanation (see above) of the language of the claims prior to the instant amendment.

Based on the foregoing amendment and clarifying remarks, fully supported in the application as filed, Applicants submit that the rejection of claims 1-9 under 35 U.S.C. § 112, second paragraph, for asserted indefiniteness has been overcome and should be withdrawn. Further, a rejection of any of new claims 10-16 under § 112, second paragraph, for indefiniteness on analogous grounds would be improper.

SUMMARY

For the foregoing reasons, each of claims 1-16 is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

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Respectfully submitted,

By 

Thomas J. Wrona, Ph.D.

Registration No.: 44,410

MARSHALL, GERSTEIN & BORUN

233 S. Wacker Drive

6300 Sears Tower

Chicago, Illinois 60606-6357

(312) 474-6300

Attorneys for Applicant